Remarks

Claims 1-4, 9-12, and 34-37 are pending in the application. Claims 34-37 have been cancelled herein without prejudice to the filing of a continuation application. Claim 30 has been cancelled herein to avoid confusion, because it was previously amended in two different responses to the previous office action that were inadvertently submitted while the case was being transferred from one law firm to another. New claim 38 duplicates claim 30 as it was presented in the response mailed 2002 by Applicant's representative on October 28, 2002. In that response, claim 30 was rewritten in independent form to include all the limitations of the base claim (previously cancelled claim 29). No new subject matter has been introduced by way of this amendment.

Claims 39, 40, and 41 have been newly added as dependent claims to claims 1, 9, and new claim 38, respectively. No new subject matter has been introduced by way of this amendment. Claims 39, 40 and 41 are supported throughout the specification as filed, particularly, at page 2, line 31 to page 3, line 3, and page 8, lines 13-26.

Response to Claim Objections

Claim 37 has been objected to because the word "oligonucleotide" in line 1 should be plural. As claim 37 has been cancelled without prejudice, the objection as to this claim is now moot.

Response to 35 U.S.C. § 112, first paragraph, written description rejection

Claims 1-4, 9-12, 30 and 34-37 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description. Claim 30 has been cancelled in lieu of new claim 38. In the interest of furthering prosecution, Applicant has cancelled 34-37 without prejudice, to the filing of a continuation application. The rejection is therefore moot as to these claims. The cancellation of claims and 34-37 should not be construed as an acquiescence on the part of the Applicant to the Examiner's position regarding these claims.

Claims 1 and 9 are drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NOS:1-4 or 5 to the substantia nigra pars reticulata or to

the internal globus pallidus via a cannula. Administration of the claimed antisense oligonucleotides down-regulates glutamic acid decarboxylase (GAD). Dependent claims 2-4 and 10-12 specify that the antisense oligonucleotides down-regulate the GAD isoforms GAD_{65}, GAD_{67}, or a combination of both.

New claim 38 is drawn to a method of downregulating GAD in any mammal *in vivo*, comprising administering an antisense oligonucleotide is directed to an initiation codon of GAD mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula, wherein the oligonucleotides comprise SEQ ID NOS:1-4 or 5.

The Examiner alleges that the specification as filed does not adequately describe a representative number of species of antisense oligonucleotides to GAD_{65} or GAD_{67} for treating Parkinson's Disease or down regulating GAD isoforms in any mammal *in vivo*.

Claims 1-4, 9-12, and 38-41 do not recite a generic antisense oligonucleotide to GAD. Rather, these claims recite the specific anti-GAD antisense oligonucleotides of SEQ ID NOS.1-5. These five antisense oligonucleotides are expressly disclosed in the present specification (see pg. 8, lns. 16-23). Methods for administering the five claimed antisense oligonucleotides to the substantia nigra pars reticulata or the internal globus pallidus in mammals via a cannula are also expressly disclosed in the present specification; see, *e.g.*, page 3, lines 4-16 and 25-30, page 4, lines 11 to page 7, line 18 and the working examples. The claimed antisense oligonucleotides and methods of administering them to mammals therefore have literal support in the specification as filed.

The Examiner asserts that the specification does not explicitly demonstrate down-regulation of the GAD mRNA targeted by the claimed antisense oligonucleotides, and thus this feature of the claims is not adequately described. However, down-regulation of GAD mRNA can be inferred from the data showing the inhibition of GAD function by the claimed antisense oligonucleotides, as compared to a control "scrambled" oligonucleotide which had no effect on GAD function *in vivo* (see Figures 4-7). In addition, the specification states at page 13, lines 13-16 that "a 2 week antisense infusion into the entopeduncular nucleus caused on average 65% reduction in GABA levels when compared with the contralateral untreated hemisphere." These data demonstrate down-regulation of GAD mRNA by showing the specific inhibition of GAD function.

The Examiner also contends that GAD downregulation with antisense oligonucleotides was shown only in two mammalian species, and therefore Applicant was not in possession of methods which down-regulate GAD in any (taken to mean "all") mammalian species. The Examiner contends that therapeutic antisense in mammals is unpredictable, and there is no clear nexus provided in the art or in the specification for believing that the present methods could be practiced on all mammals. However, one of ordinary skill in the art, based on the specification as filed and their general knowledge, would have recognized that Applicant was in possession of methods which in which the claimed antisense oligonucleotides can down-regulate GAD_{65} or GAD_{67} in any mammal.

The present specification expressly discloses that the claimed methods can be practiced on mammals, and thus there is literal support in the specification for this claim term. Figures 4, 5, 6, and 7 demonstrate that antisense oligonucleotides to GAD_{65} or to GAD_{67} can neutralize Parkinson's symptoms in such phylogenetically diverse mammals as rats and monkeys. As discussed below, the claimed antisense oligonucleotides also have a high degree of sequence identity with each other, with different GAD isoforms and with GAD genes from different mammals. Based on this, and in view of the experimental data in the present specification, one skilled in the art would accept that the claimed methods could be practiced in all mammalian species.

The Examiner is reminded that a patent application as filed is presumed to contain an adequate written description. The Examiner must therefore prove by a preponderance of the evidence that one skilled in the art would not recognize that the applicant had possession of the claimed subject matter. In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971); In re Wertheim, 191 USPQ 90, 96 (CCPA 1976). The Examiner has not provided sufficient evidence or reasons to overcome the presumption that the claimed methods can be practiced on any mammal. In contrast, the present application shows that the claimed antisense oligonucleotides are highly homologous, and provides data showing inhibition of GAD in diverse mammalian species with anti-GAD antisense oligonucleotides.

Thus, the present claims are supported by both the literal language of the specification, and by the experimental data. The Examiner has not rebutted the presumption that the present specification contains adequate written description for the claims. One skilled in the art would therefore recognize that Applicant had possession of the claimed

methods at the time the specification was filed. The 35 U.S.C. 112, 1st paragraph written description rejection of claims 1-9 and 4-12, and new claims 38-41, should be withdrawn.

Applicant respectfully points out that many of the concerns raised by the Examiner in the written description rejection appear to be enablement issues. These concerns will be more fully addressed in the following section.

Response to 35 U.S.C. § 112, first paragraph, enablement rejection

Claims 1-4, 9-12, 30, and 34-37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the administration of any antisense oligonucleotide to GAD to any mammal for the treatment of Parkinson's disease, or for the downregulation of either GAD_{65} or GAD_{67} isoform *in vivo*. The specification is allegedly enabling only for methods of treating Parkinson's disease in a rat comprising administration of the antisense of SEQ ID NO:1 to the substantia nigra pars reticulata via a cannula, or for methods of treating Parkinson's disease in a monkey comprising administration of the antisense of SEQ ID NO:5 to the internal globus pallidus via a cannula.

Claims 34-37 have been cancelled, and the rejection as to these claims is now moot. Claim 30 has been canceled in lieu of new claim 38. The enablement rejection will be discussed for claims 1-4 and 9-12 and new claims 38-41.

As discussed above, the claims do not generically recite anti-GAD antisense oligonucleotides. Rather, the claims recite the five specific antisense oligonucleotides of SEQ ID NOS:1-5. The claims are therefore do not need to be enabled for "any" (taken to mean "all") anti-GAD antisense oligonucleotides.

Because SEQ ID NOS:2-4 were not used in any animal studies, the Examiner contends that the claimed methods are not enabled for using these oligonucleotides to inhibit GAD *in vivo*. The Examiner also asserts that the homology of SEQ ID NOS:2-4 to SEQ ID NOS:1 or 5 does not provide an expectation that SEQ ID NOS:2-4 would also bind to and inhibit GAD *in vivo* in any mammal.

There is no requirement that the working examples provide the entire scope of enablement needed to support a claimed invention. Rather, the specification taken as a whole must be enabling. *In re Barr*, 170 USPQ 330 (CCPA 1971). Moreover, a specification which discloses how to make and use a claimed invention is presumed to

comply with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). Here, the Examiner has not provided sufficient reason to doubt that SEQ ID NOS:2-4 can be used in the claimed methods, or that all five claimed antisense oligonucleotides can be used to inhibit GAD or treat Parkinson's disease in any mammal.

The present specification provides sufficient guidance on how to make SEQ ID NOS:1-5 and use these oligonucleotides in the claimed methods. Once supplied with the sequences, the claimed oligonucleotides can be readily obtained or synthesized by one skilled in the art (see pg. 8, ln. 13 of the present specification). The working examples on pgs. 10-14 detail how the claimed antisense oligonucleotides can be delivered to the substantia nigra pars reticulata and internal globus pallidus in the mammalian brain via a cannula.

Also, the five claimed antisense oligonucleotides share homology with each other and with different mammalian GAD genes. For example, there is a 90.5% sequence identity between rat, pig and human GAD_{67} mRNA surrounding the target site for the claimed antisense oligonucleotides (pg. 9, lns. 7-9 of the present specification). Human anti-GAD_{67} antisense oligonucleotide SEQ ID NO: 4 can also bind to cat GAD_{67} (pg. 9, ln. 15 of the present specification). Manual analysis of mammalian GAD_{65} genes showed an 85.7% sequence identity with human GAD_{65} in the region surrounding the antisense oligonucleotide target site (see pg. 9, lns. 9-11 of the present specification). The claimed oligonucleotides also share homology with, and are expected to inhibit, different GAD isoforms (pg. 9, lns.11-15 of the present specification).

The base compositions of the claimed oligonucleotides are also similar, indicating that the oligonucleotides would have similar physical-chemical characteristics (pg. 9, lns. 16-22 of the present specification). For example, the rat GAD_{67} antisense oligonucleotide (SEQ ID NO: 1) is composed of 23.8% adenosine, 23.8% cytosine, 33.3% guanine, and 19.0% thymine. The human GAD_{67} antisense oligonucleotide (SEQ ID NO: 4) is composed

of 23.8% adenosine, 33.3% cytosine, 28.6% guanine, and 14.3% thymine. The rat GAD_{65} antisense oligonucleotide (SEQ ID NO: 2) is composed of 14.3% adenosine, 23.8% cytosine, 38.1% guanine, and 23.8% thymine. The human GAD_{65} antisense oligonucleotide (SEQ ID NO: 3) is composed of 14.3% adenosine, 28.6% cytosine, 33.3% guanine, and 23.8% thymine.

Thus, one skilled in the art would believe that SEQ ID NOS:1-5 can inhibit different GAD isoforms, and can inhibit GAD in different mammals. This is supported by the working examples, which show inhibition of GAD in rat and monkey by SEQ ID NOS:1 and 5, respectively (see Figs. 4-7).

Based on the sequence homology and experimental data reported in the specification, one skilled in the art would reasonably believe that the claimed oligonucleotides would inhibit different GAD isoforms in any mammal. The specification is therefore enabling for methods of inhibiting GAD *in vivo* or for treating Parkinson's disease by administering the SEQ ID NOS:1-5 to the substantia nigra pars reticulata or internal globus pallidus in mammals, and the 35 U.S.C. 112, 1st paragraph enablement rejection should be withdrawn.

The Examiner asserts at pages 10-14 of the Detailed Action that there is a high level of unpredictably in the art for design and use of antisense oligonucleotides to inhibit any GAD isoform in vivo via administration to any mammal for the claimed functions. The Examiner cites the following references in support of her position: Branch (TIBS, 1998, 23:45-50), Ma et al. (Biotechnology Annual Review, 2000, 5:155-196, Elsevier Science B.V., ed. M.R. El-Gewely), Flanagan et al. (Nature Biotech., 1999, 17:148-52), Jen et al. (Stem Cells, 2000, 18:307-319), Green et al. (J. Am. Coll. Surg., 2000, 191:93-105), Agrawal et al. (Molecular Medicine Today, 2000, 6:72-81), Bennett et al. (in "Methods in Molecular Medicine: Antisense Therapeutics, 1996, ed. S. Agrawal, Humana Press Inc. Totowa, NJ, pages 13-46) and McCarthy et al. (Brain Research 1994, 636:209-220).

As stated above, the claims now recite only SEQ ID NOS:1-5. The claims also recite specific delivery by catheter directly to the substantia nigra pars reticulata or internal globus pallidus. With the exception of McCarthy, none of the references cited by the Examiner involve the direct administration of antisense oligonucleotides to defined regions of the brain. McCarthy does not disclose or suggest the administration of the claimed antisense oligonucleotides to the substantia nigra pars reticulata or the internal globus pallidus. These

references are therefore not relevant to the present claims. Nevertheless, Applicant will address each reference in turn below.

Branch discusses factors which might be considered barriers to the successful delivery of antisense molecules. Ma teaches that "to gain therapeutic advantage using antisense-based technology, oligodeoxynucleotides (ODNs) must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Citing to Branch and Ma, the Examiner states at page 11 of the Detailed Action that, despite improvements in oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, ". . . the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained."

However, Branch discusses general problems relating to *systemic* administration of antisense oligonucleotides. Branch does not teach that the barriers to successful delivery outlined in that reference are relevant to *direct* administration of anti-GAD antisense molecules to specific brain structures in mammals. Ma discusses various parameters to be considered when preparing an antisense oligonucleotide, but does not teach that administering the presently claimed oligonucleotides directly to a target site produces unpredictable results. In contrast, the present specification clearly shows that direct administration of the claimed antisense oligonucleotides to the specified brain structures is successful in treating parkinsonism in mammals.

The comments in Branch and Ma that results obtained from *in vitro* studies require further experimentation to discover antisense molecules with "enhanced specificity" *in vivo* are also inapplicable here, as "enhanced specificity" is not an element of present claims. Thus, Branch and Ma are not relevant to the presently claimed methods.

Flanagan teaches that *systemically* administered oligonucleotides are not distributed and internalized equally among organs, and that target sites (such as solid tumors) contain little oligonucleotide following intravenous injections. Because the claimed invention comprises administering oligonucleotides directly to the target site, Flanagan is also not relevant to the present claims. In addition, the Flanagan citation was taken out of context.

The paragraph cited by the Examiner states that, in contrast to tissue culture studies, numerous animal studies have reported that oligonucleotides can penetrate cells and that antisense effects have been demonstrated in a variety of cell types. Flanagan further states that these animal results have helped to validate the technology for use as human therapeutics, and have resulted in several oligonucleotides entering clinical trials (see Flanagan, pg. 51, col. 2).

The Examiner cites to Ma and Flanagan to show the difficulties in the *in vivo* use of antisense oligonucleotides, thus supporting the alleged non-enablement of the present claims. As discussed above, neither Ma nor Flanagan involve the direct application of antisense oligonucleotides to the brain. These references are therefore no more relevant to the present claims in combination than they were individually.

Jen et al. state that successful application of antisense oligonucleotides in clinical trials has been "elusive," and that "most (oligonucleotides) have been characterized by a lack of toxicity, but only modest clinical effects." However, the present claims do not require any particular level of clinical efficacy, but specify only that GAD is down-regulated. As discussed above, the presently claimed oligonucleotides down-regulate GAD in mammals. Thus, Jen's concern over "elusive" clinical efficacy is not relevant here.

The Examiner cites Green for the broad proposition that the future of nucleic acid therapeutics requires "overcoming problems" (Green, pg. 103, col. 2). This citation was taken out of context, and it is inapplicable to the present claims. For example, the paragraph in Green preceding the passage cited by the Examiner reads "antisense compounds have shown efficacy in numerous preclinical studies." Green also states at pg. 103, col. 1 that "phase I trials have shown that antisense ODNs are generally well-tolerated." Thus, Green teaches that antisense oligonucleotides are generally efficacious and non-toxic.

Agrawal sets forth several "outstanding questions" regarding use of antisense oligonucleotides. However, these "outstanding questions" are also not relevant to the presently claimed invention, as Agrawal merely lists parameters to be considered when preparing and using an antisense oligonucleotide for *systemic* or *oral* administration. For example, the question in Agrawal regarding the exact mechanism of oligonucleotide uptake is not relevant here, because the present claims recite direct administration of the claimed

oligonucleotides to brain structures, and uptake into human neuronal cells *in vitro* has been demonstrated in the present working examples.

Agrawal's question regarding the mechanism of intestinal absorption of oligonucleotides and their oral bioavailability is also not applicable to the present claims, which recite the *direct* administration of oligonucleotides to brain structures.

Bennett et al. does not discuss the direct administration of the claimed antisense oligonucleotides to brain structures, but merely lists general parameters of antisense oligonucleotide preparation and their use as drugs. In fact, Bennett teaches that the relatively simple phosphorothioate modification of oligonucleotides, as recited in newly added claims 39-41, results in improvements in stability and pharmacokinetics of the oligonucleotide (Bennett et al., pg. 14 lns. 1-3).

McCarthy et al. allegedly teaches that the design and use of antisense GAD_{65} and GAD_{67} in the brain is unpredictable. However, the problems discussed in McCarthy are not applicable to the present claims, and were cited out of context. In fact, one skilled in the art would not consider McCarthy as teaching that the antisense art is unpredictable.

McCarthy administered 15-mer antisense oligonucleotides against the putative translation start codons for GAD_{65} and GAD_{67} to the medial basal hypothalamus or midbrain central gray area and modulated reproductive behavior in the female rat, but stated that uptake of an oligonucleotide into the desired cell can be a problem. However, the present specification demonstrates that the claimed antisense oligonucleotides were taken up by the cells of the internal globus pallidus and substantia nigra pars reticulata in mammals.

McCarthy also states that exogenous oligonucleotides in "high" concentrations "could" have some cellular toxicity. However, McCarthy then shows that there was no such toxicity in their studies, as antisense oligonucleotides were administered in amounts of up to 500 ng/injection directly to the target brain sites with no toxicity problems (McCarthy, pg. 217). The present specification discloses that similar amounts of the claimed oligonucleotides were used in mammals with no toxic effects.

According to the Examiner, McCarthy also shows that antisense oligonucleotides have non-specific effects. However, McCarthy merely stated that *if* non-specific effects were seen, then one would have to distinguish specific from non-specific effects (McCarthy et al., pg. 217, 2nd col., lns. 25-39). However, no such non-specific effects were reported in

McCarthy. In fact, McCarthy showed that administration of a control oligonucleotide, consisting of the same nucleotide bases but in a scrambled sequence, "did not significantly modulate behavior" when infused into any brain areas," (see McCarthy abstract).

McCarthy's studies involved oligonucleotides administered to brain sites regulating reproductive behavior, whereas the presently claimed antisense oligonucleotides are administered directly to specific sites in the brain which regulate movement (the substantia nigra pars reticulata and internal globus pallidus). Thus, as acknowledged by the Examiner on pg. 16 of the Office Action mailed May 7, 2003, McCarthy does not render the present claims obvious. However, McCarthy's success in administration of GAD antisense oligonucleotides to the brain would indicate to one skilled in the art that the presently claimed methods could be successfully practiced.

In sum, claims 1-4, 9-12, and newly added claims 38-41 are enabled by the present specification. Applicant respectfully requests that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusion

Based on the foregoing, all claims under review are believed to be in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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